INTRODUCTION

A central tenet of the developmental approach to the study of psychopathology is the idea that developing neural, physiological, and behavioral systems are self-organizing and self-regulating (Cicchetti & Tucker, 1994). Accordingly, development in any given domain of functioning, be it social-emotional, cognitive, or motor, is best understood in relation to development in other domains and as occurring through the combined action of factors operating at multiple levels of analysis, including the genetic, cellular, physiological, psychological, behavioral, and social-cultural. Also contained within the self-organizing, self-regulating view is the idea that development proceeds hierarchically, from a relatively undifferentiated to a highly differentiated state. That is, competence in a particular domain of functioning is thought to occur through a series of interdependent and adaptive steps or stages such that organization at one level, for example of genetic or hormonal processes that enable effective functioning and self-regulation at the cellular or physiological level, provides for further, more differentiated organization and self-regulation at subsequent levels (Cicchetti & Ganiban, 1986; Werner, 1957). At each level, however, opportunity for change or further constraint of developing systems may occur through feedback mechanisms in which processes leading from gene expression to behavior or from behavior to social interaction are themselves influenced by feedback resulting from organization at higher order levels. Here, the notion of compensation in development is central, as problems with organizational processes and self-regulation at a given level may lead to compensatory processes or behaviors at a higher order level that work to offset and ultimately alter developmental organization at lower order levels.

In this examination of Tourette’s syndrome (TS), we will describe how TS is a neurodevelopmental disorder...
characterized by difficulty inhibiting unwanted movements and vocalizations (tics). In describing the neurobiological basis for this difficulty, we will consider the extent to which disruptions in the structure and function of cortico-striatal-thalamic-cortico (CSTC) neural circuitry associated with tic behaviors in TS may be related to other aspects of psychological functioning associated with the voluntary control of behavior. Here, we will emphasize the point that while impairments in the control of motor function may be the most salient characteristic of the disorder, altered functioning of CSTC circuitry associated with the prefrontal cortex may also impact the cognitive and emotional development of persons with TS. Specifically, consistent with the developmental science approach to the study of psychological disorders, we will review evidence examining the extent to which TS may be characterized by general problems with inhibitory control, not only of motor function, but also in tasks requiring cognitive and emotional regulation.

DYSFUNCTIONAL MOTOR REGULATION IN TS

TS is characterized by chronic motor and vocal tics occurring every day for an extended period of time, usually beginning between the ages of 3 and 8 years (Leckman, 2002). For the majority of persons with TS, a substantial reduction in symptoms occurs after adolescence (Leckman, 2002; Pappert, Goetz, Louis, Blasucci, & Leurgans, 2003), with approximately 40% eventually becoming symptom-free (Burd et al., 2001). Motor tics can include relatively simple movements such as facial grimacing, shoulder shrugging, eye blinking, and head jerks, as well as more complex movements such as rubbing, touching, licking, or smelling. Vocal tics range from simple throat clearing to whole phrases, including obscenities and profanities (coprolalia) as well as repetition of others’ speech (echolalia). Tics are often described as semi-compulsory, as they can be suppressed for a period of time at the cost of increasing discomfort for the patient (Spessot, Plessen, & Peterson, 2004). Further, tics are usually preceded by a “premonitory urge,” described by patients as growing tension in those muscles used for the tic or an increased sense of anxiety, which is (temporarily) relieved after performance of the tic (Leckman, 2002; Leckman, King, & Cohen, 1999; Spessot et al., 2004). In this way, it is very similar to obsessive–compulsive disorder (OCD), in which subjects feel increased anxiety and discomfort until certain compulsions are performed (King, Leckman, Scähill, Cohen, 1999). Both ADHD and OCD coexist in many patients with TS (Bradshaw, 2001; Leckman, 2002), and not surprisingly it has been suggested that TS and OCD may share a common genetic susceptibility (Spessot et al.).

NEUROANATOMICAL CORRELATES OF TS

Many theories of TS have described it as a dysfunction primarily in motor inhibition involving basal ganglia circuitry (Bradshaw, 2001; Leckman, 2002; Mink, 2001; Peterson, 2001). Stimulation of the putamen in animals has been shown to evoke stereotyped movement similar to tics (Leckman, 2002). Specifically, there may be dysfunctional activity in CSTC circuits, which project from diverse areas of the cortex to the basal ganglia, through the thalamus, and back to the cortex. There are at least four (Peterson) and possibly five (Alexander, Delong, & Strick, 1986) parallel corticostriatal “loops” that are thought to gate information from the cortex in order to regulate behavior in a context-appropriate manner (Bradshaw). At least three of these loops (skeletomotor, dorsolateral prefrontal, and orbitofrontal loops) may be of particular relevance to TS. The motor loop sends excitatory projections from motor and somatosensory regions of the cortex to the putamen. From there, projections are sent to the globus pallidus (GP) and thalamus and back to supplementary motor area (SMA). The dorsolateral prefrontal cortex (DLPFC) loop sends excitatory projections to the caudate nucleus, from there running through portions of the GP and thalamus, finally returning back to DLPFC. The orbitofrontal cortex (OFC) loop originates and terminates in the OFC, also running through the caudate nucleus, GP, and thalamus (Alexander et al.). The motor circuit is thought to be involved in the regulation of movements, while the prefrontal loops may regulate more cognitive processes such as inhibition of task-irrelevant stimuli or actions, working memory, emotion regulation and impulsivity, and planning (Bradshaw). Although these loops are thought to be mostly segregated and self-regulating, there is interaction among nuclei in the basal ganglia. For example, the caudate nucleus sends inhibitory projections to other parts of the striatum including the putamen, so that increased caudate activity reduces overall activity in the motor circuit (Gerard & Peterson, 2003; Spessot et al., 2004).

Many neuroimaging studies have revealed dysfunction in various parts of the CSTC circuits. Structural imaging has revealed decreased basal ganglia asymmetry (Peterson, 2001) and decreased volume of the basal ganglia in TS patients, particularly in the caudate nucleus (Peterson et al., 1999, 2003). Increased overall volume in dorsolateral prefrontal regions in children, but not adults, with TS has been reported (Peterson et al., 2001). This increase in volume was inversely related to tic severity such that patients with greater prefrontal volumes exhibited
decreased tic severity. Finally, volumes of the corpus callosum (CC) are decreased in children with TS, correlate inversely with prefrontal volumes, and are positively related to tic severity (Plessen et al., 2004). It is likely that these findings of increased prefrontal volumes and decreased CC size represent a compensatory mechanism developed in children with TS in order to facilitate suppression of tics (Peterson et al., 2001; Spessot et al., 2004). Of interest, adults with TS tend to show the opposite pattern, exhibiting relatively decreased dorsal prefrontal and increased corpus callosum volumes that may be associated with the persistence of symptoms into adulthood (Peterson et al., 2001; Plessen et al., 2004; Margolis et al., 2006).

Indeed, in a functional neuroimaging study of tic suppression in adults with TS, decreased activity in the bilateral ventral putamen, globus pallidus, and thalamus was found during active suppression as compared to a resting state in which patients could tic freely (Peterson et al., 1998). Areas of increased activity during tic suppression were found in right midfrontal cortex, right anterior cingulate, and right ventral caudate. Further, activity in midfrontal regions was positively correlated with activity in the caudate, and caudate activity was inversely correlated with activity in the putamen, globus pallidus, and thalamus, consistent with the known excitatory projections from the cortex to the caudate nucleus and inhibitory projections from the caudate nucleus to other basal ganglia structures.

Braun et al. (1995) found a relation between activity in OFC and putamen and severity of behavioral symptoms in TS adults using positron emission tomography (PET). Individuals with TS were categorized based on severity of behavioral symptoms including self-injurious behavior (SIB), impulsivity, ecophenomena, coprolalia, obsessive–compulsive behavior, and depression. Significant positive correlations were found between regional metabolic activity in bilateral orbitofrontal cortices and putamen and behavioral severity scores. Additionally, poorer performance on neuropsychological tests of attention including the digit span, digit symbol, simple processing in healthy controls has implicated both the DLPFC and OFC in the successful inhibition of task-irrelevant stimuli, responses, or impulses (Berlin, Rolls, & Kischka, 2004; Braver, Barch, Gray, Molfese, & Snyder, 2001; Konishi et al., 1999; Metzler & Parkin, 2000). The emergence of inhibitory control, defined as the suppression or overriding of highly learned prepotent responses or distracting stimuli that can interfere with the effortful allocation of attention within a specific task context, is a central aspect of cognitive development (Diamond, 2002). It is also one that has been shown to be impaired in a wide variety of developmental disorders (Zelazo & Müller, 2002). Research into inhibitory processing in healthy controls has implicated both the DLPFC and OFC in the successful inhibition of task-irrelevant stimuli, responses, or impulses (Berlin, Rolls, & Kischka, 2004; Braver, Barch, Gray, Molfese, & Snyder, 2001; Konishi et al., 1999; Metzler & Parkin, 2000). Primarily this has been shown using Stroop, Simon, and Eriksen flanker tasks, which require subjects to respond according to one feature of a stimulus while ignoring conflicting information (Eriksen & Eriksen, 1974; Simon, 1990; Stroop, 1935). In these tasks, subjects must selectively attend to task-relevant information while
ignoring task-irrelevant information. Interference from task-irrelevant information may arise from the attended stimulus itself, as in the Stroop and Simon tasks, or from distractors located near to the attended stimulus, as in the flanker task. Neuroimaging studies using these tasks have suggested that activity in DLPFC is related to directing attention to task-relevant information while ignoring distractors (Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002; MacDonald, Cohen, Stenger, & Carter, 2000; Milham, Banich, & Barada, 2003; Peterson et al., 2002; van Veen, Cohen, Botvinick, Stenger, & Carter, 2001).

Another task used to measure cognitive inhibition, negative priming (NP), occurs when subjects are slower to respond to a stimulus that was ignored on the previous trial. NP is thought to reflect a measure of pure cognitive inhibition without the influence of motor systems (Fox, 1995; Tipper & Cranston, 1985) and has been found to be dependent on the integrity of frontal cortex (Metzler & Parkin, 2000). Neuropsychological tests of executive functioning that examine inhibitory control, such as the Hayling task, have also highlighted the role of the prefrontal cortex in inhibition. In the Hayling test, subjects complete a series of sentences first with appropriate words (e.g., “London is a big...,” “city”), and then with nonsensical words (e.g., “London is a big...,” “banana”), so that successful completion of the second part of the test requires that subjects inhibit responding with the appropriate word (dominant response). Performance of this task has been shown to involve activation in regions of the anterior cingulate, inferior frontal gyrus, and middle frontal gyrus (Collette et al., 2001; Nathaniel-James, Fletcher, & Frith, 1997) and is impaired in patients with frontal lobe lesions (Burgess & Shallice, 1996).

Although the majority of research indicates that an impairment in visuomotor integration (e.g., when copying simple geometric designs) (Schultz, Carter, Seahill, & Leckman, 1999), continuous performance (Shucard, Benedict, Tekok Kilic, & Lichter, 1997), and habit learning (Keri, Szlobodnyik, Benedek, Janka, & Gadoros, 2002; Marsh et al., 2004) is found in patients with TS, comparatively fewer studies have consistently found deficits in cognitive inhibition in TS. However, given the deficit in motor inhibition and its probable link to dysfunction in circuits involving prefrontal cortex, it would be surprising if cognitive inhibition was not impaired to some extent in patients with TS. Recent reviews have suggested that TS patients perform normally on standard tests of executive functioning, and that, the majority of impairments are found in patients with comorbid ADHD (Brand et al., 2002; Muller et al., 2003; Ozonoff & Jensen, 1999; Pennington & Ozonoff, 1996; Sherman, Shepard, Joschko, & Freeman, 1998; Silverstein, Como, Palumbo, West, & Osborn, 1995). However, a few studies controlling for comorbid disorders have found selective impairments on inhibition tasks among TS patients. In one study, patients with TS alone performed normally on neuropsychological tests of fluency but exhibited an increase in intrusion errors on verbal list learning (Mahone, Koth, Cutting, Singer, & Denckla, 2001). Channon, Sinclair, Waller, Healey, & Robertson (2004) compared the performance of adults with TS alone with that of age-matched controls on a variety of cognitive tasks including those testing inhibition (Hayling test), set-switching, and multitasking. Results indicating that the TS group made significantly more errors on the Hayling test of inhibition but not on other tests of executive functioning suggest the presence of a relatively circumscribed inhibitory deficit, consistent with other reported increases in errors among TS patients on the Hayling Test but not on other tests of executive function (Channon, Crawford, Vakili, & Robertson, 2003; Channon, Pratt, & Robertson, 2003). At least two experiments have examined the performance of TS patients in NP paradigms (Ozonoff, Strayer, McMahon, & Filloux, 1998; Swerdlow, Magulac, Filion, & Zinner, 1996). One (Ozonoff et al.) presented TS and control children with five-letter strings to which they made button-press responses depending on whether the second and fourth (task-relevant) letters were the same or different. The other three flanking letters were distractors and were always identical. On ignored repetition (negative priming) trials, at least one of the task-relevant letters on trial \( N \) was used as a distractor on trial \( N - 1 \), while on neutral trials task-relevant letters were novel. Results indicated that control subjects were slower to respond on ignored repetition trials as compared to neutral trials, exhibiting the standard NP effect. The performance of the TS group overall was not significantly different from that of the control group, although RT variability on NP trials was found to be higher among TS patients. However, when the TS group was segregated according to comorbidity with ADHD and OCD, there was a trend for TS patients who had another disorder to show less NP than TS alone or controls, indicative of an impairment in cognitive inhibition. Finally, overall severity of symptoms from all disorders (TS, ADHD, and OCD) were used to segregate the patients into those with high or low symptom severity. While there were no differences in mean RT between high severity, low severity, and control subjects, the control and low severity group showed evidence of NP but the high severity group did not. Although the precise comorbidity status of the newly-formed high and low severity groups was not reported, the authors stated that approximately 25% of patients changed groupings from when they were segregated only according to diagnoses (i.e., a proportion of TS alone patients fell into the high severity category and TS patients with another disorder...
fell into the low severity category). Thus, it is unlikely that this effect was driven solely by the comorbidity status of the TS patients.

In another study involving adults and children with TS and age-matched controls (Swerdlow et al., 1996), participants were required to press one of four computer keys corresponding to a target spatial location. Four lines designating spatial locations were arranged on a computer screen; on each trial an “X” and an “O” were presented above two of the lines. Subjects pressed the key that corresponded to the location of the “O” and ignored the location of the “X.” The location of the “O” on trial N could be the same as the location of the “X” on trial N + 1 (NP trials) or unrelated (neutral trials). Results indicated that both adults and children with TS exhibited less NP than controls, an effect that only approached significance in adults but was highly reliable in children. In contrast to the findings of Ozonoff et al. (1998), no effect of disorder comorbidity was found with ADHD, OCD, conduct disorder, oppositional defiant disorder, or elimination disorder, and no significant relationship between symptom severity and NP scores was found.

Further support for the notion that inhibition of task-irrelevant information is impaired in TS patients is provided by work using a Simon task (Georgiou, Bradshaw, Phillips, Bradshaw, & Chiu, 1995). Adult TS patients and control subjects were presented with an arrow located either to the left or right of the center and were required to make a button-press response according to the direction of the arrow head. The direction of the arrow was either congruent with spatial location (e.g., a rightward pointing arrow located to the right of center) or incongruent (e.g., a rightward pointing arrow located to the left of center). The classic Simon effect, where subjects are slower to respond on incongruent as compared to congruent trials, was greater for TS patients than for controls, again suggesting the presence of an inhibitory deficit extending into cognitive functioning. Interestingly, however, the Simon effect was not found in control subjects at all, thus raising some concern about the validity of this measure in assessing inhibitory processes. Further, the comorbidity of the patient group was not documented, so the impact of other disorders or performance cannot be ruled out.

In a cohort of adolescents with TS without comorbid disorders and age-matched controls, Crawford, Channon, and Robertson (2005) assessed performance on two tests of cognitive inhibition—sentence completion and flanker—as well as working memory and reward learning tasks. In the sentence completion task, subjects were first required to finish sentences with words that made sense (part A) before completing the same sentences with nonsensical words (part B). In order to assess whether participants with TS exhibited greater difficulty inhibiting highly automatic (as opposed to minimally automatic) responses, as would be expected if a selective deficit in inhibitory control existed, the authors used two levels of completion prepotency in part A. Half of the sentences were those in which 99% of a sample population consistently answered one word (prepotent condition) while the other half had multiple completions, all of which made sense but none of which were particularly dominant (nonprepotent condition). In the flanker task, subjects responded according to the direction of a centrally presented arrow (left or right) which was flanked by surrounding arrows pointing in the same direction (congruent trials) or the opposite direction (incongruent trials). Whereas performance on working memory and reward learning tasks were equivalent for the TS and controls groups, performance on the tests of inhibition, indicated the presence of a mild impairment on some, but not all, aspects of inhibitory control. For the sentence completion task, TS patients made more errors and performed more slowly on nonsensical completions (part B) as compared to controls, however, the expected increase in errors and RT or part B for TS patients associated with the more prepotent condition of part A was not obtained. Thus, patients were overall less accurate and slower than controls, yet these effects were not dependent on the amount of inhibitory control that was required, and thus may reflect executive deficits not specific to inhibition. However, on the flanker task TS patients made significantly more errors and had were slower on incongruent trials as compared to control subjects. In addition, ratings of tic severity were correlated with RT such that those patients with greater symptoms were slower to respond, perhaps indicative of a deficit in inhibiting the distracting flankers. A later study by the same group obtained similar results examining adult TS patients without comorbid disorders (Channon, Gunning, Frankl, & Robertson, 2006). While TS patients again exhibited increased errors on nonsensical completions in part B irrespective of ending prepotency in part A, impaired performance on the flanker task was not replicated.

Results from these studies provide some support for the suggestion that cognitive inhibition is impaired in patients with TS, although such evidence has not been found consistently. Differing results may be due in part to the motor requirements of the paradigms employed. Arguably, the Simon and flanker tasks require a greater amount of motor inhibition than sentence completion and negative priming tasks. In many cases, TS alone may not be sufficient to impair cognitive inhibition, with deficits emerging when TS occurs in combination with other disorders involving corticostriatal dysfunction (i.e., ADHD or OCD). Further, it is possible that cognitive deficits are more pronounced in TS children as compared with adults. Healthy children show reduced NP as compared to adults.
AFFECTIVE REGULATION IN TS

Along with motor and cognitive inhibition, successful social functioning often involves inhibition of contextually inappropriate emotions. There have been reports of higher incidence of episodic rage outbursts (Budman, Bruun, Park, Lesser, & Olson, 2000; Budman, Rockmore, Stokes, & Sossin, 2003) and SIB (Mathews et al., 2004) in patients with TS, perhaps due to abnormalities in the functioning of the OFC (Braun et al., 1995). Damage to the OFC has long been linked with personality disturbances, aggression, and impulsivity (Berlin et al., 2004; Malloy, Bihlre, Duffy, & Cimino, 1993; Rolls, Hornak, Wade, & Megrath, 1994; Spinella, 2004). Animals with lesions to the OFC are impaired on tasks of response inhibition (Passingham, 1972) and show increased emotional reactivity (Sato, 1971). In humans, orbitofrontal lesions have been associated with increased anger and reduced happiness, higher scores on self-report and cognitive-behavioral measures of impulsivity, and greater difficulty responding to changed reward contingencies (Berlin et al.).

Episodic rage attacks have been reported in approximately 25% of TS cases (Budman et al., 2000, 2003; Rosenberg, Brown, & Singer, 1995) and appear to be more common in children with TS and in persons with TS with a comorbid disorder (Budman et al., 2000; Sukhodolsky et al., 2003). These explosive outbursts of anger are not consistent with the usual mood and demeanor of the patient, and are grossly out of proportion to any precipitating event. Interestingly, patients often report experiencing an increasing sense of tension and arousal prior to onset of rage attacks, similar to the premonitory urge that often precedes tics (Budman et al., 2000).

Mathews et al. (2004) found that 29% of a large cohort of children and adults with TS had SIB (defined as deliberate, self-directed behavior resulting in tissue damage or injury such as head banging, persistent skin picking, or scratching) while 4% had severe SIB (defined as behavior that could result in permanent injury such as self-cutting, eye-poking, or head banging resulting in concussion). Predictors for severe SIB included episodic rage attacks and risk-taking, suggesting that affective dysregulation contributes significantly to severe SIB when it occurs in TS.

CONCLUSIONS

Although not specifically addressing the question of affective regulation, there has been some evidence that emotions are processed abnormally in patients with TS with comorbid OCD (Johannes et al., 1999). Adult patients and controls were presented with positive, negative, or neutral words. Two-thirds of the words were repeated, and subjects were required to discriminate whether each trial was the first or second presentation of a given word. Event-related potentials (ERPs), scalp-recorded voltage changes measuring post-synaptic potentials from a group of synchronously active neurons, were recorded from subjects in order to examine cortical activity associated with the processing of repeated emotional and neutral words in TS/OCD patients. Among both controls and patients, there was greater amplitude at frontal-central electrodes between 350 and 550 ms post word presentation for repeated neutral words as compared to novel neutral words (termed the “old–new” effect), consistent with prior studies (Rugg & Nagy, 1989). For both positive and negative words, control subjects also showed the old–new effect. By contrast, patients showed a significantly smaller old–new effect for positive words and no effect at all for negative words. Although localization of neural sources is difficult given the relatively low spatial resolution of ERPs, these results suggest that a frontal mechanism involved in encoding information about words for later recognition is impaired for emotional stimuli only in TS/OCD patients.

Although TS is often considered to be a disorder primarily of motor inhibition, there is modest evidence to suggest that cognitive and affective regulation are also impaired in persons with the disorder. Cognitive inhibitory deficits among patients with TS have been found in a variety of neuropsychological and experimental paradigms, including sentence completion, negative priming, and interference tasks. Inconsistencies are clearly present in the literature, which may be partially attributable to the sensitivity of the task used to measure inhibition, age of the patient, and comorbidity status. Specifically, it seems that the most reliable predictor of cognitive impairment in patients with TS is the presence of another disorder involving altered frontal functioning (ADHD or OCD) or frontal lobes that are not fully developed (children). Affective dysregulation is found frequently, with explosive rage attacks and/or SIB occurring in at least one-fourth of children with TS. While comparatively little research has addressed the neural correlates of emotional processing in TS, it is likely that dysfunction in orbitofrontal basal ganglia circuitry contributes in part to the problems of impulsivity and rage attacks.
Although inhibitory motor deficits in TS might be expected to lead to more general problems with cognitive and social self-regulation, a developmental approach suggests otherwise. In particular, the developmental approach suggests that compensatory processes occurring over time and in response to motor inhibition deficits could work either to offset or to exacerbate cognitive and social self-regulation deficits in persons with TS. Thus, mixed results across studies may reflect heterogeneity in neurobiological development or personal experiences among patients with TS. Age of onset in the disorder is typically early, at approximately 5–7 years of age, with symptoms attenuating by adulthood for a substantial proportion of cases. One hypothesis concerning the differentiation of persons for whom symptoms attenuate from those who retain symptoms into adulthood concerns the development of frontal cortical top-down control of motor deficits. Specifically, given the relatively protracted course of the development of the prefrontal cortex and processes of use-dependent synaptic plasticity, it is likely that attenuation of the disorder is due to compensatory developmental neurobiological processes. Prefrontal cortical volumes in children with TS have been found to be larger than those in adult patients (Peterson et al., 2001), suggesting that frontal plasticity in childhood may be important for understanding the severity and course of the disorder.

From a developmental standpoint, it makes sense to also ask whether or not variation in cognitive inhibitory control or impulse inhibition in TS is associated with the unique experiences of the patient during the course of the disorder. Here, it is important to consider the developmental process as it occurs in response to the psychosocial environment in which the individual is situated in addition to constraints imposed by the neurobiological motor deficit. Such an approach can increase understanding of longer-term outcomes and also suggest some potentially efficacious therapies to improve quality of life for patients with TS. Only through prospective longitudinal research beginning in early childhood can relations among brain structure, brain function, behavior, and environment be satisfactorily addressed in the study of TS. By acquiring longitudinal data using multiple neuroimaging modalities, the specific neurological deficits, behaviors, and environments associated with either increasing severity or with compensation and remediation of behavioral deficits can be identified.

REFERENCES


Stern, Blair, and Peterson


